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Continuous Infusion May Improve the Efficacy of Vancomycin in Treatment of Experimental Endocarditis Due to Heterogeneous Vancomycin-Intermediate *Staphylococcus aureus*

We read with interest the paper of Entenza and coworkers suggesting failure of continuous vancomycin infusion against experimental endocarditis due to heterogeneous vancomycin-intermediate *Staphylococcus aureus* (hVISA) and VISA (1).

In that study, it was stated that continuous vancomycin infusion for 5 days was unsuccessful, as 20 mg/liter was barely active against hVISA PC1 (6 of 13 sterile vegetations) and 40 mg/liter failed against VISA PC3 (2 of 9 sterile vegetations). Generally speaking, we agree that in this experimental model vancomycin led to suboptimal treatment of VISA infection; however, we believe that some findings related to the role that continuous infusion may have in improving the outcome of vancomycin treatment of hVISA infections deserve attention.

Indeed, in the hVISA PC1 model (vancomycin MIC, 2 mg/liter), there was a misinterpretation of the results, since it appears from Fig. 1 in that paper that the number of sterile vegetations obtained by continuous infusion was higher than stated (7/13 and not 6/13). More importantly, compared with intermittent vancomycin administration (peak and trough levels of at least 50 and 10 mg/liter, respectively), continuous infusion with a constant serum drug concentration of 20 mg/liter was significantly more effective in sterilizing hVISA PC1 vegetations (54% versus 18%, $P < 0.05$). Although fewer than 100% of the vegetations were sterilized, it must be highlighted that continuous infusion was the only bactericidal regimen, since it led to a more-than-4-log reduction of the mean bacterial burden in the vegetations at day 5 compared to that in the controls (3.57 ± 2.1 versus 7.64 ± 0.4 $\log_{10}$ CFU/g [$P < 0.001$]), which is different from what occurred with intermittent infusion (6.82 ± 3.1 $\log_{10}$ versus 7.64 ± 0.4 $\log_{10}$ CFU/g [no statistically significant difference]).

These data suggest that continuous infusion of vancomycin may significantly improve the treatment outcome of experimental endocarditis due to hVISA. Indeed, the incomplete sterilization seen even after 5 days of continuous vancomycin infusion may be in line with the time-dependent activity of this glycopeptide, which may take a much longer time for complete healing to occur, especially if the bacteria are embedded in biofilm (2). However, it is worth noting that by ensuring that the concentration persistently exceeds a value of at least four to five times the MIC, this strategy may also reduce the selective pressure due to very low trough levels (3) and may avert the development of frank vancomycin resistance, even in cases of long-term treatment (4).

Considering that a recent systematic review and meta-analysis of the clinical significance of hVISA isolates (5) showed that hVISA infections were associated with a glycopeptide failure rate 2.37-fold greater than that obtained with vancomycin-susceptible *S. aureus* infections, we do believe that these experimental data may support the idea that continuous infusion may be worthwhile with the intent to decrease the failure rate of vancomycin treatment of humans with hVISA infections.

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Federico Pea*
Piergiorgio Cojutti
Institute of Clinical Pharmacology & Toxicology
Azienda Ospedaliero-Universitaria Santa Maria della Misericordia, Udine
Department of Experimental and Clinical Medicine
Medical School, University of Udine
P. le S. Maria della Misericordia 3
33100 Udine, Italy

Nicola Petrosillo
2nd Infectious Diseases Division
National Institute for Infectious Diseases Lazzaro Spallanzani
Rome, Italy

Mario Furlanut
Institute of Clinical Pharmacology & Toxicology
Azienda Ospedaliero-Universitaria Santa Maria della Misericordia, Udine
Department of Experimental and Clinical Medicine
Medical School, University of Udine
P. le S. Maria della Misericordia 3
33100 Udine, Italy

*Phone: 39 0432 559833
Fax: 39 0432 559819
E-mail: pea.federico@aoud.sanita.fvg.it

Authors' Reply

We thank Pea et al. for their comment on our article on the efficacy of continuous vancomycin infusion against experimental endocarditis due to vancomycin-intermediate *Staphylococcus aureus* (VISA) (2). Pea et al. dispute our interpretation that continuous vancomycin infusion was poorly effective against both heterogeneously resistant VISA (hVISA) and homogeneously resistant VISA. They consider that the relative activity of continuous vancomycin infusion against hVISA in animals indicates that it might also be useful in humans. In brief, our data show that sequential (twice a day) vancomycin treatment was successful in animals infected with vancomycin-susceptible *S. aureus* but completely failed against hVISA (vancomycin MIC = 2 mg/liter) and VISA (vancomycin MIC = 8 mg/liter). In comparison, continuous infusion providing constant serum drug levels of 10 times the MIC tended to be more effective against hVISA (ca. 50% cure rate) but also failed against VISA (ca. 20% cure rate). Moreover, in spite of some activity, continuous infusion selected for derivatives of both hVISA and VISA with increased resistance levels.

We do agree with the first assertion of Pea et al. that

continuous vancomycin infusion had some activity against hVISA. This is specifically stated in the article as follows: "The present study demonstrates that continuous infusion of vancomycin, at concentrations affording optimal constant serum levels of 10 times the MIC for the infecting organism, was more effective than standard sequential treatment but relatively not optimal against experimental endocarditis due to hVISA." On the other hand, we do not share their optimism about the safe use of such a regimen in clinics. Indeed, similar experimental results (regarding limited success and resistance selection) were previously obtained with quinolones and precisely predicted the later occurrence of treatment failures and resistance selection with these drugs in humans (1, 3). Therefore, we do not recommend continuous vancomycin infusion as an optimal choice for use against hVISA because its limited success and especially the prompt selection of resistance make it unsafe.

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J. M. Entenza*
T. R. Veloso
J. Vouillamoz
M. Giddey
P. Moreillon
Department of Fundamental Microbiology
Biophore—University of Lausanne
CH-1015 Lausanne, Switzerland

*Phone: 41-21-6925612
Fax: 41-21-6925605
E-mail: jose.entenza@unil.ch